## Circulating endothelial and progenitor cells during anti-angiogenic treatment in cancer patients

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# CHAPTER 4

## SUNITINIB-INDUCED HEMOGLOBIN CHANGES ARE RELATED TO THE DOSING SCHEDULE

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# TO THE EDITOR:

We read with interest the correspondence by Alexandrescu *et al.* [1] reporting the occurrence of erythrocytosis in 5 out of 21 patients treated with sorafenib or sunitinib. We also observed erythrocytosis during sunitinib treatment, although we detected that hemoglobin and erythrocyte changes occurred in a cyclic pattern. In an expanded access programme (EAP), 82 patients with metastatic renal cell cancer (mRCC) were treated with sunitinib 50 mg daily (4-week-on/2-week-off) [2]. We measured hemoglobin levels on day 1 and 28 of each cycle and on day 14 of the first cycle. In 90% of patients we observed a transient rise in hemoglobin during the first cycle. The median hemoglobin level of 7.5 mmol/L (range 5.2-10.4 mmol/L) at baseline increased to 8.4 mmol/L (range 6.0-10.9 mmol/L; Wilcoxon signed rank, $p < 0.001$) on day 14 and 8.0 mmol/L (range 5.7-10.7 mmol/L; $p < 0.001$) on day 28 of the first cycle. After the 2-week rest period, the median hemoglobin level returned to baseline of 7.8 mmol/L (range 5.2-10.0 mmol/L; $p = 0.127$). This transient rise in hemoglobin occurred in all following cycles (Fig 1). In 69% of patients, the maximum level was reached during the first cycle (range: cycle 1 to cycle 10) with a median increase of 1.2 mmol/L. In 46 patients in the EAP, hemoglobin-associated variables, including hematocrit, erythrocytes, MCV, MCH and MCHC, as well as Vascular Endothelial Growth Factor (VEGF) were available (Table 1). The incidence of erythrocytosis (erythrocytes above the upper limit of normal) was 26% during the first cycle, while a significant increase in erythrocyte numbers occurred in 81% of these patients.

The cyclic kinetics in hemoglobin values and erythrocyte numbers indicates that sunitinib scheduling is the cause of these changes. Thus far, its mechanism is not known. Tam et al [3] have described that neutralization of VEGF in mouse and primate models can result in an increase in the secretion of erythropoietin from the liver, leading to erythropoiesis and erythrocytosis. Another study in mice has demonstrated that sunitinib can increase erythropoietin levels [4]. Therefore, we measured erythropoietin at baseline and on day 14 of the first cycle in 20 unselected patients and indeed found an increase from a median of 12 U/L (range: 1.2-119.9) to 26 U/L (range: 12.9-54.2) ($p < 0.002$). Although the difference in erythropoietin levels is significant, an erythropoietin-induced increase in erythrocytes is not expected to diminish rapidly within the 2 weeks of rest.

We here propose another mechanism for the transient hemoglobin changes during sunitinib treatment. Like other inhibitors of VEGF signaling, sunitinib is known to raise blood pressure [5]. In 39 of our patients blood pressure was consistently monitored with a Dinamap (Dash 4000, GE Medical Systems Information Technologies, Inc., Milwaukee, Wisconsin, U.S.A.). In these patients we detected a significant rise in blood pressure on day 14 and 28 of the first cycle, which was reversible after the rest period (Table 1). On

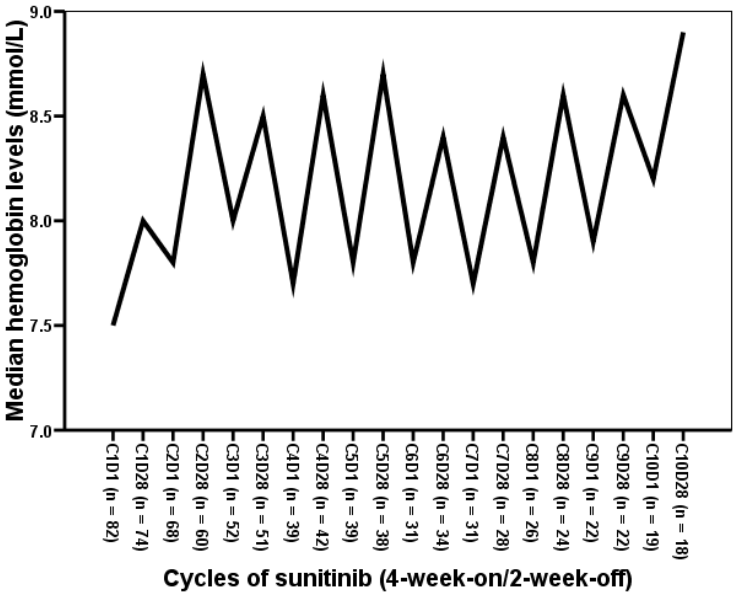


**Figure 1 - Median hemoglobin levels during the first ten cycles of sunitib treatment. C, cycle; D, day.**

day 28, changes in mean arterial blood pressure (MAP) were significantly correlated with changes in hemoglobin levels (Spearman's $\rho = 0.552$, $p = 0.004$, n = 25).

Sunitinib-induced rise in blood pressure is thought to be caused by increased peripheral resistance [6, 7]. VEGFR-2 plays a role in the regulation of the vascular tone, since inhibition of the VEGFR-2 signaling route may decrease the production of the potent vasodilator nitric oxide (NO) leading to vasoconstriction [8, 9]. In rats, Filep [10] has previously described that inhibition of NO synthase increased blood pressure and hematocrit, lowered plasma volume, and induced albumin escape primarily in the lung, heart, liver, kidney and gastrointestinal tract. In 67 out of 82 patients baseline albumin levels were available; albumin decreased during sunitinb treatment (from a median of 41 G/L to a median of 38 G/L on day 28, $p < 0.001$, n = 67) and increased after the rest period (from 38 G/L to 40 G/L, $p = 0.002$, n = 67). Loss of circulating plasma volume is a likely cause for the relative rise in hemoglobin, hematocrit and erythrocytes by sunitinib.

In summary, we describe a 'zig-zag' pattern in hemoglobin levels and erythrocyte numbers during sunitinib treatment in mRCC patients. Based on previous studies and our findings, we hypothesize that the cyclic kinetics of hemoglobin and erythrocytes is the

result of a temporary loss of intravascular fluid caused by inhibition of VEGFR-2 and subsequent reduction of NO rather than an increase in erythropoiesis.

**Table 1.** Changes in hemoglobin-associated variables, VEGF and blood pressure during the first cycle of sunitinib treatment

| Variable | C1D1 | | | C1D14 | | | C1D28 | | | C2D1 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | median | range | n | median | range | n | median | range | n | median | range | n |
| Hemoglobin (mmol/L) | 7.5 | (5.4-10.6) | 46 | 8.2*** | (6.2-10.6) | 46 | 8.0* | (5.3-10.4) | 31 | 7.0* | (5.2-9.4) | 39 |
| Hematocrit | 0.36 | (0.27-0.48) | 45 | 0.39*** | (0.32-0.51) | 45 | 0.39* | (0.25-0.50) | 30 | 0.33** | (0.25-0.46) | 36 |
| Erythrocytes ($x10^{12}$/L) | 4.4 | (3.1-8.5) | 42 | 4.7*** | (3.7-6.7) | 42 | 4.6* | (2.9-5.6) | 30 | 4** | (2.8-5.6) | 33 |
| MCV (fL) | 85 | (68-94) | 41 | 84* | (68-93) | 42 | 85 | (74-93) | 30 | 87*** | (69-97) | 33 |
| MCH (amol/cell) | 1762 | (1198-2023) | 41 | 1787 | (1260-1936) | 42 | 1815 | (1465-1955) | 30 | 1843*** | (1266-2023) | 33 |
| MCHC (mmol/L) | 20.8 | (17.7-23.2) | 41 | 20.8 | (18.1-22.4) | 42 | 20.8 | (18.7-22.5) | 30 | 20.9 | (18.3-22.2) | 33 |
| VEGF (pg/mL) | 70 | (21-650) | 30 | 258*** | (57-1722) | 32 | 210*** | (45-1499) | 22 | 70 | (34-300) | 21 |
| Systolic BP (mm Hg) | 120 | (93-170) | 39 | 139*** | (105-189) | 38 | 137** | (108-178) | 25 | 119 | (86-149) | 32 |
| Diastolic BP (mm Hg) | 71 | (47-90) | 39 | 80*** | (56-114) | 38 | 83** | (69-105) | 25 | 70 | (48-99) | 32 |
| MAP (mm Hg) | 90 | (69-117) | 39 | 101*** | (73-138) | 38 | 100*** | (83-129) | 25 | 85 | (67-113) | 32 |

Abbreviations: MCV, mean corpuscular volume; MCH, mean cellular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; VEGF, Vascular Endothelial Growth Factor; BP, blood pressure; MAP, mean arterial pressure, MAP = P*diastolic* + 1/3(P*systolic* - P*diastolic*)

*$p \leq 0.05$, compared to baseline value by the Wilcoxon Signed Ranks test

**$p \leq 0.01$, compared to baseline value by the Wilcoxon Signed Ranks test

***$p \leq 0.001$, compared to baseline value by the Wilcoxon Signed Ranks test

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